REMARKS/ARGUMENTS

Claim status. Claims 28, 29, 40, 46-51, and 63-71 remain pending. Claim 46 has been amended. Claims 72-79, which the Examiner withdrew from consideration, are canceled hereby. No claims have been added.

Support for amendments. All amendments to the specification and claims are supported in the application as originally filed, as explained below.

The amendment to the paragraph at page 1, line 2, merely adds the status of the applications cited, as requested by the Examiner in the last office action. The amendment to Claim 46 merely clarifies the intended meaning and is well understood from the specification.

Objection to specification. The Office Action objected to the specification for incorporation of material by reference to WO patent applications. The cited WO patent applications, however, do not relate to the claimed subject matter of the subject patent application. The references in question describe the preparation of peptides that appear in the subsequent tables. None of those peptides are described as modulating the activity of AGP-3, which is required by the broadest claim pending (Claim 46), so the disclosure of the cited references is not essential and need not be incorporated.[1]

General remarks on grounds for rejection. The Applicants attempt below to address each of the points raised in the Office Action. Before addressing these points in detail, the Applicants would like the Examiner to bear in mind the following general considerations.

The Examiner diligently reviewed the extensive specification and numerous references provided in this application. In the current Office Action, however, the Examiner seemed to view the claimed invention through the prism of the Russel reference rather than analyzing the invention on its own terms. The Russel reference is intended to provide information on carrying out a phage display project (see page 1 thereof). The authors are concerned with the problems encountered in displaying proteins of interest, such as intracellular proteins or heterodimeric proteins, in phage (see page 11). Their focus is thus on library formation. Library formation is compatible with and not excluded by the claimed process, but the claimed process *does not*

[1] Even if the claims did not have the limitation to AGP-3 modulating activity, amendment to the specification would not be required. The sequences of the peptides is given in the specification, and their preparation is known in the art. No subject matter

require library formation as a step of the process. The claimed process concerns what is done with peptides identified from a phage display library, not the development and content of the library itself.

Another recurring theme in the Office Action is a focus on the structure of peptides identified in the process. The Examiner seems to regard the process as a poorly described rational drug design process. Phage display does allow a form of rational design called affinity maturation, in which the artisan selects certain residues for mutagenesis while holding others constant through repeated rounds of library generation and screening. Affinity maturation is compatible with and not excluded by the claimed process, but the claimed process *does not require affinity maturation as a step of the process.* Indeed, the very power of peptide display technology is that, like antibody development, it allows one to identify peptides by functional property alone (i.e., binding to the target protein of interest), without need to design the structure beforehand.

The Applicants request that the Examiner instead consider the invention on its own terms. In particular, the Examiner's attention is directed to the following excerpt from the specification:

> Peptides identified by peptide library screening have been regarded as "leads" in development of therapeutic agents rather than as therapeutic agents themselves. Like other proteins and peptides, they would be rapidly removed in vivo either by renal filtration, cellular clearance mechanisms in the reticuloendothelial system, or proteolytic degradation. Francis (1992), Focus on Growth Factors 3: 4-11. As a result, the art presently uses the identified peptides to validate drug targets or as scaffolds for design of organic compounds that might not have been as easily or as quickly identified through chemical library screening. Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24; Kay *et al.* (1998), Drug Disc. Today 3: 370-8. The art would benefit from a process by which such peptides could more readily yield therapeutic agents.

(Specification at page 11, lines 2-13). The claimed process should be analyzed not as a process for phage library generation, not as a process for affinity maturation or rational peptide structural design, but rather as a process by which such peptides could more readily yield therapeutic agents that modulate AGP-3.

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disclosed in such references and absent from the specification (other than by incorporation by reference) is included in the claims. Thus, the specification need not be amended.

112, first paragraph: Written Description. The Office Action argued, "The disclosure at the time of filing does not describe the huge scope of the claimed components in the method." The Office Action then objected in particular to the definition of peptide as including from 2 to 40 amino acids. For support of the rejection, the Examiner cited *In re Riat*, 140 USPQ 471 (1963); *In re Barr*, 170 USPQ 330 (1971); and *Univ. Calif. v. Eli Lilly*, 43 USPQ 2d 1398 (1997).

The rationale of the Office Action is contrary to the factual basis for the invention. The Applicants' claimed process can be understood by analogy to a process for obtaining antibodies. Antibodies are obtained by binding to a target molecule. It is that *function*, rather than the underlying structure of the antibodies, that is used in the process to identify and isolate the antibodies. Antigen binding is not a vague biological property, but a specific functional property that identifies the antibodies as different from all other antibodies. Antibodies of course have a structure, but that structure is determined after they have been isolated and not as part of the process for generating them. Likewise, the claimed process uses essentially the same functional property—binding to a target molecule—to identify the peptides used in the compounds produced by the process. Those peptides are later linked to an Fc domain to make the compounds produced by the process. Unlike small molecule development, one does not design molecules by specific structure[1] and then assay for binding; instead, a diverse library of peptides is screened for binding to a protein of interest. To require the Applicants to define the structure of the peptides in the claims is to require a different process than they actually use.

The Office Action's rejection further requires a level of predictability that is neither practical nor called upon by patent law. Step (a) of Claim 46 is a peptide library screening step. Would the Examiner require a claim to a small molecule screening assay to define the structure of small molecules that could be selected by it? Would the Examiner require an antibody screening claim to define the CDR sequences of selected antibodies? Step (a) is in fact carried out by a functional screen and thus correctly limited by a functional parameter.

The rationale of the Office Action is also inconsistent with the case law. All three cases concern claims to compositions of matter rather than processes. This difference is significant: In the *UC v. Lilly* case, the patent applicants sought protection for composition of matter genera defined by the terms "vertebrate" and "mammalian" without reciting any structure or formula to define such genera. Even in the quoted passage from *University of California v. Eli Lilly*, the court makes clear that their holding concerns the written description of a chemical genus.

Here, the Applicants claim a process rather than a composition of matter. The steps of the process, not the peptides resulting from step (a) of the process, are the elements that should have an adequate written description. The Office Action questions not the adequacy of that description, but rather the description of the products of this process, which are not claimed. The Office Action's rationale would deny a screening assay claim because the Applicant could not predict the structure of each molecule identified in such a screen; if that rationale prevailed, no screening assay claim would be patentable.

More important, the actual terms in the claims do have written description support. The Examiner correctly did not object to selecting a peptide from a phage display library. That process is well described in the references cited in the specification and the Information Disclosure Statement, including Scott *et al.* (1990), Science 249: 386; Devlin *et al.* (1990), Science 249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No. 5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12, 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665, issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998. Furthermore, the Applicants have provided extensive working examples of peptides selected by phage display and of the claimed process.

Furthermore, as noted above, the Office Action's reliance on Russel *et al.* is misplaced. The passage quoted by the Office Action is as follows:

> ...[S]ome sequences will be refractory to display and therefore under represented in the displayed library in the extreme. The *optimal* clone (e.g., the one with the highest affinity) may never be isolated because it fails to display. (emphasis added).

Russel *et al.* discuss display of the *optimal* clone; they do not suggest that the selection process will fail to identify molecules that bind to a target. Their concern is library formation, which is not a required step of Claim 46. Furthermore, even if one accepts Russel *et al.*'s proposition as correct, all they state is that some sequences (sequences "refractory to display") might not be selected in the process. The Applicants claim a process that includes selecting peptides *from* a peptide phage display library; they don't claim every peptide *in* such a library or every peptide that someone attempted to include in such a library. Most important, Russel *et al.* are actually discussing phage display of variants of a natural protein, cautioning that the optimal variant of

[1] The claimed process allows--but does not require--structural modification by affinity maturation.

the natural protein may fail to display; these authors take as a given that peptides are suitable for phage display. (See Russel *et al.*'s section entitled, "Feasibility of display," page 11, *et seq.*).

Section 112, first paragraph: Enablement. The Office Action cited the eight-factor *Wands* test and alleged that the specification did not provide adequate direction and guidance because "It does not describe the kind, type, location and length of peptide in peptide phage display library that is a modulator of a protein of interest." (Office Action at page 8). As noted above, the Office Action persists in requiring structural features to a step that is in fact accomplished by functional means. Step (a) of Claim 46 clearly and simply requires "selecting from a peptide phage display library at least one peptide sequence that modulates the activity of AGP-3." As noted above, this functional parameter comes directly from the nature of the process itself. Would the Examiner require a claim to a small molecule screening assay to define the structure of small molecules that could be selected by it? Would the Examiner require an antibody screening claim to define the CDR sequences of selected antibodies? Step (a) is in fact carried out by a functional screen and thus correctly limited by a functional parameter.

The Office Action alleged that the Applicants failed to provide working examples for any of the "numerous and different type of techniques" that can be used. The Office Action provided no further discussion of this point. For step (a), the Applicants cite the hundreds of peptides provided in the specification that were identified by selection from a peptide phage display library for other target proteins. The phage display selection of these is well documented in the cited references, so there is no need to provide working examples repeating such disclosures. See, for example, the references cited in Table 2 at page 6 of the specification. For step (b), the Applicants refer to the specification at Example 2 (TPO-mimetics), pages 99-111; Example 3 (EPO-mimetics), pages 111-117; Example.4 (TNF antagonists), pages 117-120); Example 5 (IL-1 antagonists), pages 120-123; Example 6 (VEGF antagonists), pages 123-126; and Example 7 (MMP inhibitors), pages 126-127. Each of these working examples explicitly describes not just one but many embodiments of step (b) as carried out for other target proteins. These extensive references and working examples overwhelmingly refute the Office Action's allegation of failure to provide working examples.

The Office Action cited breadth of claims, again mentioning lack of structure of the peptides (page 8 of the Office Action). The Office Action discussed difficulties in peptide design, such as determining where to make insertions. The Office Action's argument is based on Russel *et al.*, which addresses formation of particular libraries for such purposes as altering

properties of existing proteins (see Russel *et al.*'s introduction at page 1). The claimed process, in contrast, does not include library formation as a step. Random peptide libraries were known in the art prior to the filing of the present application (see the references cited in the specification at page 3, lines 3-9). Step (a) of the claimed process can be carried out with such libraries, with no need for the artisan to know the structure of the peptides displayed in such a library. Any difficulties in custom library formation are irrelevant to claim 46.[1]

The Office Action also noted, without further explanation, "The state of the prior art is such that techniques are specifically applied for a predetermined protein, phage display library." (Office Action at page 9). Here again, the Office Action focuses on difficulties in custom library formation, which is not part of the claimed process.

The Office Action also alleged the art to be unpredictable, citing Russel *et al.* Here, the Office Action appeared to argue that one could not predict the sequence of peptides selected or, more likely, the sequence of peptides displayed in a library. The argument is inapposite and in conflict with the art. As noted above, the Applicants do not seek and do not claim that step (a) will identify peptides with a predetermined sequence. The Office Action misapplies Russel *et al.*'s discussion on library formation to the Applicants' step of selection from a library. The hundreds of peptides selected by phage display cited in the application and the dozens of references describing their selection refute any argument that peptide selection is unpredictable.

Section 112, second paragraph. The Office Action alleged a "lack of correspondence" between steps (a) and (b). Specifically, the Office Action asked whether the formula in step (b) represented the molecules selected in step (a) or whether the "P" substituents in the formula represented the sequences selected in step (a). The answer is the latter: the peptide sequences in step (a) are incorporated into the molecule having the formula shown in step (b). In the interest of compact prosecution, Claim 46 is amended to make that immediately apparent.

The Office Action's section on Section 112, second paragraph also requested structural definition of the peptides selected in step (a). In response, the Applicants refer to the remarks hereinabove.

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[1] A skilled artisan need not actually design a peptide, but rather can randomly mutagenize one or all of the sequences of whatever peptides used for initial library generation. The power of the technology is that it circumvents the very problems that the Examiner finds intractable. See, for example, U.S. Pat. No. 5,223,409.

Double Patenting. In this section, the Office Action alleged double patenting over the co-pending sister applications. Prosecution on those applications has continued and in some applications will continue, such that the claims will not overlap. In particular, three of the applications have since been allowed and claim only compositions of matter. The claimed process clearly is not overlapping with the applications claiming compositions of matter applications, as it is not overlapping with the granted patent in this family (U.S. Pat. No. 6,660,843).

The Office Action also alleged that there is no apparent reason why the currently prosecuted claims were not presented during the prosecution that matured into the patent (U.S. Pat. No. 6,660,843). To the contrary, the prosecution that led to the patent included an extensive restriction requirement that did not allow the current claims to be pursued therein.

Other co-pending applications claim processes of different scope from the process claimed in this application. Two such applications claim processes directed to different targets, such that the claimed subject matter does not overlap. The '286 application claims are of different scope from the subject application. The Applicants will include an appropriate terminal disclaimer if the law requires, keeping in mind that the different scope allowed may render such terminal disclaimer unnecessary.

Section 103. The Office Action rejected the claims over Chamow, *TIBTECH*, in view of Staten *et al.*, WO 97/12978 "or applicants' disclosure of known prior art, alone" (Office Action at page 13). These references fail to include any suggestion for their combination and do not, even in combination, suggest the Applicants' claimed process.

The Staten reference (WO 97/12978) is cited in the Office Action only for certain linkers. It includes no teaching relevant to step (a) or step (b) of Claim 46.

The Chamow *et al.* reference is a review article on immunoadhesins. The authors define an immunoadhesin as "an antibody-like molecule that fuses the Fc region of an immunoglobulin and *the ligand-binding region of a receptor or adhesion molecule*." (Chamow *et al.* at page 52, emphasis added). They further clarify, "Several strategies ... have been pursued to circumvent the difficulty in obtaining human mAbs....A fourth strategy, which is the subject of this review, is to generate an antibody-like molecule by combining framework sequences from a human mAb with sequences from a *human protein* that carries a target-recognition function." (page 52,

emphasis added). Table 1 of the reference lists more than 50 immunoadhesins, all of which have Fc linked to naturally occurring proteins (page 54).

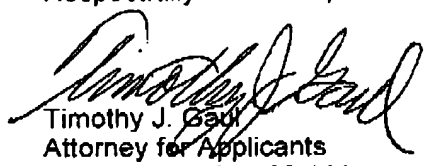
By its own terms, the Chamow reference makes the Applicants' case *for* patentability—the authors' definition considers only natural proteins linked to Fc. Their extensive review shows that only natural protein-Fc fusions had been reported. The claimed process, in contrast, requires selection of peptides from a library, and such libraries can be formed by random mutagenesis. Chamow *et al.*'s review article, however, shows that those in the art had not considered combining peptide library selection and Fc fusion.

The Office Action also seized upon the Applicants' non-controversial statements on use of techniques known in the art, statements with which the Examiner apparently agrees. These statements support enablement and do not render the claimed process obvious. Although one may use known techniques to make them, the art simply did not suggest making the molecules defined by the structure shown in step (b) of Claim 46. The prior art further did not suggest using peptides selected by peptide phage display (step (a) of Claim 46) in molecules defined by the structure shown in step (b) of Claim 46. The Applicants, not the prior art, put together the claimed process.

CONCLUSION. In light of the foregoing amendments and remarks, the Applicants respectfully request entry of all amendments and allowance of all claims.

The Commissioner is hereby authorized to charge any filing fees that may be required or credit any overpayment to Deposit Account No. 01-0519 in the name of Amgen Inc.

Respectfully submitted,



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